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Effect of change in sequence of administration of DTwP and Hepatitis B vaccines on perception of pain in infants: A randomized control trial

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ABSTRACT

Objective: This study was designed with objective to study pain response of infants to change in sequence of administration of Hepatitis B and DTwP vaccines.
Methods: This was a randomized parallel control trial. The study was carried out in the immunization clinic of the Department of Pediatrics, LLRM Medical College, Meerut. One hundred and thirty healthy term infants up to 4 months of age were injected either DTwP vaccine first or Hepatitis B vaccine first, followed one minute later by the other vaccine.
Result: Baseline characteristics did not differ between the groups. The mean (SD) of AUC of MFCS and NIPS was significantly more in DF group as compared to HF group (for MFCS 25.5 ± 5.4 versus 22.5 ± 5.5, $p < 0.01$; for NIPS 31.77 ± 5.5 versus 27.64 ± 6.9, $p < 0.01$). Similarly mean (SD) of AUC of Heart rate and saturation of oxygen showed significant variation in DF group as compared to HF group (for heart rate 591.6 ± 55 versus 559.6 ± 49, $p < 0.01$; for SpO_2 326.4 ± 12 versus 335 ± 8, $p < 0.01$).
Conclusion: These results showed that infant experienced lesser pain when Hepatitis B was administered first than when DTwP vaccine was given first.

1. Introduction

Vaccination is the most common procedure causing undue pain in an infant. It is associated with increased anxiety, avoidance and parent distress [29]. Although it may not be possible to completely eliminate pain in infants, measures to reduce the amount and intensity of pain is important not only because it is an ethical parental expectation but also because repeated painful exposures can have deleterious consequences [4,10,27]. Growing scientific and clinical evidence from both animal and human infant points to the efficacy of natural, non-pharmacologic interventions in reducing pain due to minor procedures [5]. Although effective pain relief is now usually provided for infants during and after a major surgical procedure, pain-reducing therapies are often underused for the numerous minor procedures like vaccination that are a part of routine medical care for infants [12]. With the advent of more and more vaccines, multiple inoculations in a visit is a reality despite more vaccines now being available as combinations. In addition, numerous non-pharmacological and pharmacological intervention, simple sequence of vaccine administration is a procedural technique that can potentially reduce pain in infants. Studies with some vaccine have shown that their co-administration in a particular order result in reduced pain perception [15,24]. Though Hepatitis B first dose is recommended at 4 week and DTwP at 6 week, they are often given together at 6 weeks. This happens if Hepatitis B was delayed in first or second dose due to any reason. Though hexavalent vaccine with DPT/HiB/Hepatitis B is available in developed countries, it is not available in India. So they have to be given separately. We, therefore, designed a study to evaluate if the sequence or order of administration of first DTwP and Hepatitis B has impact on perception of pain in young infants up to 4 months of age.

2. Methods

2.1. Study design and setting

This study was designed as a randomized parallel group active controlled trial. After approval from Institutional Ethical

Abbreviations: DTwP, diphtheria tetanus whole cell pertussis vaccine; DF, DTwP first vaccinated; AUC, area under the curve; HF, Hepatitis B first vaccinated; IQR, interquartile range; MFCS, Modified facial coding system; NIPS, Neonatal facial coding system; SD, standard deviation.

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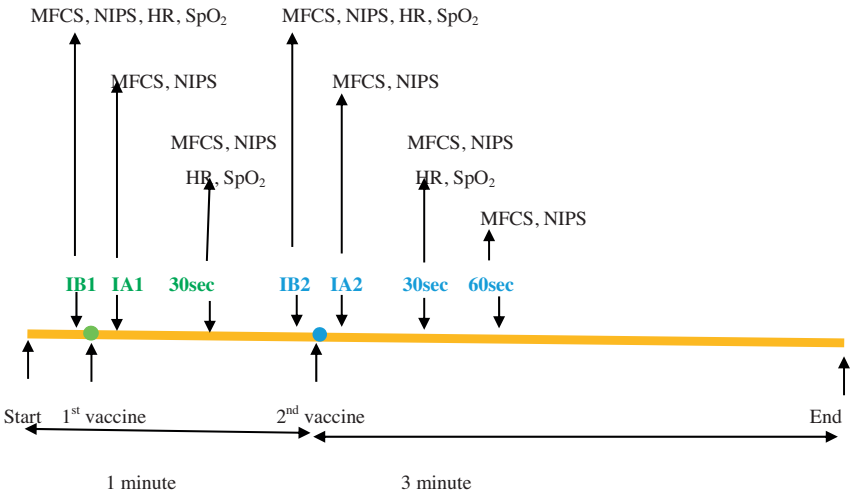

IB1 – Immediately before 1st vaccine injection**:** Parameter observed or analysed **-** MFCS, NIPS, HR, and SpO_2.

IA1- Immediately after 1st vaccine injection**:** Parameter observed or analysed **-** MFCS, NIPS.

30 sec- 30 seconds after 2nd vaccine injection**:** Parameter observed or analysed **-** MFCS, NIPS, HR, and SpO_2.

IB2- Immediately before 2nd vaccine injection**:** Parameter observed or analysed **-** MFCS, NIPS, HR, and SpO_2.

IA2- Immediately 2nd vaccine injection**:** Parameter observed or analysed **-** MFCS, NIPS.

30 sec- 30 seconds after 2nd vaccine injection**:** Parameter observed or analysed **-** MFCS, NIPS HR, and SpO_2.

60 sec- 60 seconds after 2nd vaccine injection**:** Parameter observed or analysed **-** MFCS, NIPS

NIPS – Neonatal Infant Pain Scale

MFCS – Modified Facial Coding System

HR – Heart rate

SpO_2 – Saturation of oxygen

Fig. 1. Timeline of the study.

Committee, this study was carried out in the Immunization Clinic of Department of Pediatrics, LLRM Medical College, Meerut, India. *Trial Registration:* This trial was registered at clinical trial registry of India (CTRI/2014/11/005207).

2.2. Participants

Healthy full term infants, up to 4 months of postnatal age, were enrolled who attended immunization clinic for first DTwP vaccine and any dose of Hepatitis B vaccine as per the immunization program. Exclusion criteria were: infants who were admitted in hospital for more than 48 h, perinatal asphyxia (1 min Apgar score <7) or delayed cry (duration >5 min) if born at home, small for gestational age, pre-term (<37 week of gestation), previous surgery or any major congenital anomaly.

2.3. Randomization

2.3.1. Sequence generation, allocation and concealment

Infants were randomly allocated to 1 of 2 groups in a 1:1 ratio by block randomization with computer-generated randomly permuted blocks of 8. The numbers were written on small slips and placed in sequentially numbered opaque sealed envelopes (SNOSE METHOD). Random sequence was generated by an independent statistician using online software generated random number list with URL http://www.sealedenvelope.com. The subjects were randomized into two groups:

(i) HF group—Hepatitis B vaccination prior to DTwP vaccination.
(ii) DF group—DTwP vaccination prior to Hepatitis B vaccination.

The sealed envelopes were opened in a separate room by the staff on duty. The staff loaded the two syringes with DTwP and Hepatitis B vaccine and labeled 'first' and 'second' according to order in the slip over opaque tape. The doctor received two labeled syringes and injected vaccines in order, firstly injecting vaccine labeled as 'first' and one minute later the other vaccine labeled as 'second'.

2.3.2. Intervention and blinding

After explaining the full procedure, written consent was taken from caretakers in their local language. Babies were brought to the room where vaccination was to be done. Infants were comfortably placed on immunization table in supine position. The demographics, clinical characteristics and hemodynamic parameters of all